

Table e-1. Time on study in ENDORSE

Characteristic	Continued DMF ^a		New to DMF ^a			
	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Total number of patient-years of follow-up	1545.1	1512.6	688.1	653.8	299.5	281.6
Time on study, mean (SD) months ^b	40.2 (13.1)	39.4 (14.2)	36.0 (16.6)	34.4 (17.1)	33.1 (15.1)	30.9 (17.4)
Patients on study for at least, n (%)						
6 months	490 (98)	484 (97)	225 (90)	219 (88)	108 (92)	103 (87)
1 year	472 (94)	465 (93)	208 (84)	205 (83)	101 (86)	91 (76)
2 years	445 (89)	431(86)	195 (78)	189 (76)	88 (75)	78 (66)
3 years	389 (78)	376 (75)	173 (69)	152 (61)	72 (61)	73 (61)
4 years	141 (28)	142 (28)	61 (24)	55 (22)	18 (15)	16 (13)
5 years	15 (3)	20 (4)	7 (3)	9 (4)	0	0

^aDMF, delayed-release DMF.

^bOne month is equivalent to four weeks.

BID, twice daily; DMF, dimethyl fumarate; GA glatiramer acetate; PBO, placebo; SD, standard deviation; TID, thrice daily.

Table e-2. Baseline demographics of the MRI cohort in ENDORSE and at start of DEFINE and CONFIRM

Characteristic ^a	Continued DMF ^b			New to DMF ^b		
	BID/BID (n=211)	TID/TID (n=221)	PBO/BID (n=104)	PBO/TID (n=102)	GA/BID (n=48)	GA/TID (n=60)
Start of ENDORSE						
Age, years	40.4 (8.8)	39.7 (9.1)	39.7 (8.7)	40.5 (9.1)	38.6 (8.2)	40.5 (9.2)
Female, n (%)	155 (73)	159 (72)	77 (74)	71 (70)	37 (77)	36 (60)
Start of DEFINE and CONFIRM						
Relapses in prior year	1.3 (0.7)	1.3 (0.6)	1.3 (0.7)	1.4 (0.8)	1.3 (0.6)	1.3 (0.6)
EDSS score	2.4 (1.2)	2.4 (1.1)	2.5 (1.1)	2.5 (1.2)	2.4 (1.2)	2.6 (1.4)
Gd+ lesion number	2.1 (5.5)	1.4 (3.2)	1.4 (2.4)	1.6 (3.1)	1.4 (2.1)	2.6 (7.0)
T2 lesion volume (cm ³)	11.0 (11.5)	11.1 (13.7)	8.4 (8.2)	10.2 (12.4)	13.5 (11.1)	15.3 (17.3)
T1 lesion volume (cm ³)	3.4 (4.8)	3.3 (4.9)	2.4 (3.1)	3.4 (5.6)	2.9 (3.6)	3.5 (4.9)

^aValues are mean (SD) unless otherwise stated.

^bDMF, delayed-release DMF.

BID, twice daily; DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium enhanced; MRI, magnetic resonance image; PBO, placebo; SD, standard deviation; TID, thrice daily.

Table e-3. Safety overview in ENDORSE

Events, n (%) ^b	Continued DMF ^a			New to DMF ^a		
	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Any AE	454 (91)	459 (92)	237 (95)	231 (93)	104 (88)	101 (85)
Serious AEs	109 (22)	124 (25)	59 (24)	40 (16)	19 (16)	23 (19)
AEs leading to discontinuation of study drug	28 (6)	36 (7)	42 (17)	41 (17)	16 (14)	31 (26)
Occurring within <6 months	7 (1)	14 (3)	32 (13)	36 (15)	11 (9)	21 (18)
Infections	327 (65)	322 (64)	141 (57)	139 (56) ^c	61 (52)	55 (46)
Serious infections	18 (4)	13 (3)	8 (3)	7 (3) ^c	2 (2)	4 (3)
Malignancy	10 (2)	8 (2)	5 (2)	0	0	3 (3)
Deaths ^c	2 (<1)	2 (<1)	1 (<1) ^d	0	0	0

^aDMF, delayed-release DMF.

^bIncidence represents cumulative incidence throughout the observation period.

^cAfter the May 2014 data cut-off, a fatal case of PML was reported in the setting of severe, prolonged lymphopenia (approximately $<0.5 \times 10^9/L$ of 3.5 years duration) in a PBO/TID patient; no other deaths were reported after this data cut. No other deaths were assessed by investigators as being related to study drug. Percentages are based on the ITT population.

^dOccurred after withdrawal from the study.

AE, adverse event; BID, twice daily; DMF, dimethyl fumarate; GA, glatiramer acetate; ITT, intention-to-treat; PBO, placebo; PML, progressive multifocal leukoencephalopathy; TID, thrice daily.

Table e-4. AEs leading to treatment discontinuation with an incidence $\geq 1\%$ in any treatment group

Events, n (%) ^b	Continued DMF ^a		New to DMF ^a			
	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Discontinued due to any AE	28 (6)	36 (7)	42 (17)	41 (17)	16 (14)	31 (26)
Flushing	1 (<1)	2 (<1)	9 (4)	4 (2)	2 (2)	1 (<1)
MS relapse	4 (<1)	5 (<1)	2 (<1)	0	2 (2)	2 (2)
Upper abdominal pain	0	0	8 (3)	4 (2)	0	3 (3)
Diarrhea	0	1 (<1)	4 (2)	5 (2)	4 (3)	1 (<1)
Nausea	1 (<1)	0	2 (<1)	6 (2)	2 (2)	3 (3)
Abdominal pain	0	0	4 (2)	2 (<1)	2 (2)	5 (4)
Vomiting	0	0	0	3 (1)	4 (3)	4 (3)
Pruritus	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (2)	0
Urticaria	0	0	1 (<1)	2 (<1)	2 (2)	1 (<1)
Dyspepsia	0	0	3 (1)	1 (<1)	1 (<1)	0
Hot flush	0	1 (<1)	0	3 (1)	0	2 (2)
GI disorder	0	0	1 (<1)	3 (1)	0	0
Dyspnea	0	0	3 (1)	1 (<1)	0	0
Vertigo	0	0	0	0	2 (2)	0
Increased hepatic enzyme	0	0	1 (<1)	0	0	2 (2)
Increased	0	2 (<1)	1 (<1)	2 (<1)	2 (2)	0

Events, n (%) ^b	Continued DMF ^a			New to DMF ^a		
	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
GGT						
Increased ALT	1 (<1)	2 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (2)
Increased AST	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	2 (2)
Breast cancer	3 (<1)	3 (<1)	0	0	0	2 (2)

^aDMF, delayed-release DMF.

^bIncidence represents cumulative incidence throughout the observation period.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DMF, dimethyl fumarate; GA, glatiramer acetate; GGT, gamma-glutamyl transferase; GI, gastrointestinal; MS, multiple sclerosis; PBO, placebo; TID, thrice daily.

Table e-5. Malignancies reported in ENDORSE

Events, n (%)	Continued DMF ^a		New to DMF ^a			
	BID/BID (n=501)	TID/TID (n=501)	PBO/BID (n=249)	PBO/TID (n=248)	GA/BID (n=118)	GA/TID (n=119)
Malignancies	10 (2)	8 (2)	5 (2)	0	0	3 (3)
Breast cancer	3 (<1)	3 (<1)	0	0	0	2 (2)
Malignant melanoma	1 (<1)	2 (<1)	0	0	0	0
Renal cell carcinoma	1 (<1)	0	1 (<1) ^b	0	0	0
Renal neoplasm ^c	1 (<1)	0	0	0	0	0
Thyroid cancer	1 (<1)	1 (<1)	0	0	0	0
Anal cancer	1 (<1)	0	0	0	0	0
Breast cancer <i>in situ</i>	0	0	1 (<1)	0	0	0
Endometrial cancer	0	0	1 (<1) ^b	0	0	0
CML	0	1 (<1)	0	0	0	0
Glioma	0	0	1 (<1)	0	0	0
Lung carcinoma	1 (<1)	0	0	0	0	0
Mesothelioma	0	0	1 (<1)	0	0	0
Rectal cancer	0	0	0	0	0	1 (<1)
Salivary gland cancer	0	1 (<1)	0	0	0	0
SCC	0	0	1 (<1)	0	0	0
SCC of cervix	1 (<1)	0	0	0	0	0

^aDMF, delayed-release DMF.^bReported in the same patient

^cFurther specified as a renal cell carcinoma on histology records

BID, twice daily; CML, chronic myeloid leukemia; DMF, dimethyl fumarate; GA, glatiramer acetate; PBO, placebo; SCC, squamous cell carcinoma; TID, thrice daily.